

Design and Synthesis of HIF-1 Inhibitors as Anti-Cancer Therapeutics

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Hypoxia, or reduced of oxygen pressure, in healthy cells leads to cell necrosis and reoxygenation injuries; however, hypoxia is a prominent property of most solid tumors. The low oxygen pressure in cells activates the hypoxia-inducible factor (HIF) family of transcription factors, which induce targets genes that regulates adaptive biological processes such as anaerobic metabolism, cell motility and angiogenesis¹. Overexpression of HIF-1 α , a subunit of the HIF complex, has been linked to metastasis of tumor cells, and resistance to radio and chemotherapy. Because of this, HIF-1 has become an important therapeutic target for the inhibition of tumor growth by small molecules. It is our goal to design and synthesize novel small-molecules that disrupts HIF pathway mainly by targeting the HIF-1 α subunit to prevent it from binding with the HIF-1 β subunit that makes the HIF heterodimer and initiate its biochemical activity as a transcription factor that promote tumor cell growth. Mechanistic studies shows that these novel inhibitors do not primarily alter HIF-1 levels rather, they interfere with the HIF complex formation¹. An initial HRE-alkaline phosphatase assay screening was done to find a lead compound.

A compound (KCN-1) with an IC₅₀ of 0.4 μ M was tested and was found to be very potent in decreasing tumor size. Optimization of the said compound was subsequently done by dividing the compound into 4 parts (cores) and analogues have been made; the best compound made to date has an IC₅₀ of 0.25 μ M.

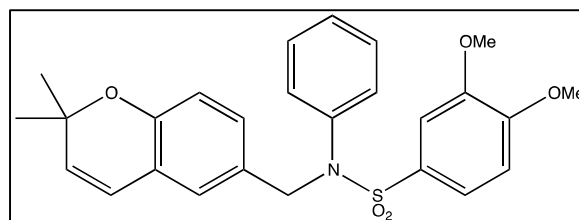


Figure 1 Molecular Structure of KCN-1

References:

1. Mooring, S.R.; Jin, H.; Devi, N.S.; Jabbar, A.A.; Kaluz, S.; Liu, Y.; Van Meir, E.G.; Wang, B., Design and Synthesis of Novel Small-Molecule Inhibitors of the Hypoxia Inducible Factor Pathway. *Journal of Medicinal Chemistry* **2011** 54 (24), 8471-8489.